X.. + plasmid
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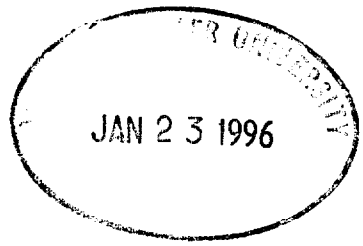

Dr. Joshua Lederberg
The Rockefeller University
1230 York Avenue
New York, NY 10021-6399

Dear Dr. Lederberg:

Imagine my surprise and delight to receive your communication in this morning's mail. I am not altogether sure since I was dressing at the time, but I believe that you were interviewed on the CNN morning news today. To answer your question about the extrachromosomal DNA review paper, there are several caveats that need to be made. "Analysis of cloned eccDNA fragments or total eccDNAs have shown that all eccDNAs share homologies with chromosomal DNA." This is misleading in part. The part concerning cloned sequences is correct. Excluding viruses and plasmids (and for mammalian cells there appear to be no plasmids), all cloned/sequenced extrachromosomal DNAs have their counterparts in the chromosome. However, we do not know if **all** extrachromosomal sequences have a chromosomal complement. What I meant to say is that every chromosomal sequence that has been probed for in eccDNAs has been found, but these surveys have been limited to repetitive sequence families because low-copy sequences are much more difficult to detect. I don't know that anyone has ever attempted to find non-chromosomal sequences in eccDNAs, at least not in a systematic, exhaustive manner. Furthermore, I am not aware of any eccDNA work done with mammalian germ cells, embryonic cells yes, but not germ cells. Therefore, the question "Are all eccDNA sequences also in the chromosomes?" is open. Recent work on replication origins and autonomously replicating sequences in mammalian cells indicates that only relatively larger DNA fragments (>50 kb) are capable of replicating extrachromosomally. This would tend to eliminate most, but not all, eccDNAs from independent replication. Viral infections of germ cells would indeed be expected to extend the haploid content of sequences, perhaps by extrachromosomal mechanisms. Retroviral infections have most assuredly added to the complement of pseudogenes and repetitive sequences, including endogenous retroviruses. The impact of germ-line DNA virus infections has not been explored as much as retroviruses; although it is known that DNA viruses promote chromosomal instability in somatic and germ cells and increase the quantity of non-viral eccDNA sequences in somatic cells.

I hope some of the above is useful to you, and I enclose a copy of a review chapter on aging and genomic instability that you might find of interest. Please keep up the good work.

Best Wishes,

Jim Gaubatz

James W. Gaubatz, Ph.D.

Mol. Basis of Aging